PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing: 28 October 1999 (28.10.99)	
International application No.: PCT/AU99/00294	Applicant's or agent's file reference: 40126941
International filing date: 20 April 1999 (20.04.99)	Priority date: 22 April 1998 (22.04.98)
Applicant: WAI-CHIU SO, Tony et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

13 September 1999 (13.09.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

NOONAN, Greg
Freehills Carter Smith & Beadle
101 Collins Street
Melbourne, VIC 3000
AUSTRALIE

Date of mailing (day/month/year)
03 July 2000 (03.07.00)

Applicant's or agent's file reference
40126941

IMPORTANT NOTIFICATION

International application No.
PCT/AU99/00294

International filing date (day/month/year)
20 April 1999 (20.04.99)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

NOONAN, Greg
Freehills Patent Attorneys
Level 47
101 Collins Street
Melbourne, VIC 3000
Australia

State of Nationality

State of Residence

Telephone No.
613-9288-1577

Facsimile No.
613-9288-1567

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

NOONAN, Greg
Freehills Carter Smith & Beadle
101 Collins Street
Melbourne, VIC 3000
Australia

State of Nationality

State of Residence

Telephone No.
613-9288-1577

Facsimile No.
613-9288-1567

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

Th International Bureau of WIPO
34, chemin des C lombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Christine Carrié

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003388053

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* **40126941**

Box No. I TITLE OF INVENTION

Pharmaceutical composition

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Soltec Research Pty Ltd
8 Macro Court
Rowville, Victoria 3178
AUSTRALIA

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: **Australia**

State *(that is, country)* of residence: **Australia**

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated*

WAI-CHIU SO, Tony
7 Marsden Crescent
Doncaster East, Victoria 3109
AUSTRALIA

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(if this check-box is marked, do not fill in below).*

State *(that is, country)* of nationality: **Australia**

State *(that is, country)* of residence: **Australia**

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

NOONAN, Greg
CHERRY, James
DI GIANTOMASSO, Frank
CALLINAN, Keith
JONES, Paul
DAVY, John
TULLOCH, Debra

Freehills Patent Attorneys
Level 47
101 Collins Street
Melbourne, Victoria 3000
AUSTRALIA

Telephone No. **(613) 9288 1577**

Facsimile No. **(613) 9288 1567**

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DEO, Peter Paul
3/119 Atkinson Street
Oakleigh, Victoria 3166
AUSTRALIA

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(if this check-box is marked, do not fill in below).*

State *(that is, country)* of nationality: **Australia**

State *(that is, country)* of residence: **Australia**

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TAIT, Russell John
33 Campbell Road
Deepdene, Victoria 3103
AUSTRALIA

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(if this check-box is marked, do not fill in below).*

State *(that is, country)* of nationality: **Australia**

State *(that is, country)* of residence: **Australia**

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(if this check-box is marked, do not fill in below).*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(if this check-box is marked, do not fill in below).*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STAT

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ **AE** United Arab Emirates .....
- ☒ **AL** Albania .....
- ☒ **AM** Armenia .....
- ☒ **AT** Austria .....
- ☒ **AU** Australia .....
- ☒ **AZ** Azerbaijan
- ☒ **BA** Bosnia and Herzegovina .....
- ☒ **BB** Barbados
- ☒ **BG** Bulgaria .....
- ☒ **BR** Brazil .....
- ☒ **BY** Belarus .....
- ☒ **CA** Canada
- ☒ **CH and LI** Switzerland and Liechtenstein
- ☒ **CN** China .....
- ☒ **CU** Cuba .....
- ☒ **CZ** Czech Republic .....
- ☒ **DE** Germany .....
- ☒ **DK** Denmark .....
- ☒ **EE** Estonia .....
- ☒ **ES** Spain .....
- ☒ **FI** Finland .....
- ☒ **GB** United Kingdom
- ☒ **GD** Grenada .....
- ☒ **GE** Georgia .....
- ☒ **GH** Ghana .....
- ☒ **GM** Gambia
- ☒ **HR** Croatia
- ☒ **HU** Hungary .....
- ☒ **ID** Indonesia .....
- ☒ **IL** Israel .....
- ☒ **IS** Iceland
- ☒ **IN** India
- ☒ **JP** Japan .....
- ☒ **KE** Kenya .....
- ☒ **KG** Kyrgyzstan .....
- ☒ **KP** Democratic People's Republic of Korea .....
- ☒ **KR** Republic of Korea .....
- ☒ **KZ** Kazakhstan .....
- ☒ **LC** Saint Lucia
- ☒ **LK** Sri Lanka
- ☒ **LR** Liberia
- ☒ **LS** Lesotho .....
- ☒ **LT** Lithuania
- ☒ **LU** Luxembourg
- ☒ **LV** Latvia
- ☒ **MD** Republic of .....
- ☒ **MG** Madagascar .....
- ☒ **MK** The former Yugoslav Republic of Macedonia .....
- ☒ **MN** Mongolia
- ☒ **MW** Malawi .....
- ☒ **MX** Mexico .....
- ☒ **NO** Norway
- ☒ **NZ** New Zealand .....
- ☒ **PL** Poland .....
- ☒ **PT** Portugal .....
- ☒ **RO** Romania
- ☒ **RU** Russian .....
- ☒ **SD** Sudan
- ☒ **SE** Sweden
- ☒ **SG** Singapore
- ☒ **SI** Slovenia
- ☒ **SK** Slovakia .....
- ☒ **SL** Sierra Leone
- ☒ **TJ** Tajikistan .....
- ☒ **TM** Turkmenistan .....
- ☒ **TR** Turkey .....
- ☒ **TT** Trinidad and .....
- ☒ **UA** Ukraine .....
- ☒ **UG** Uganda .....
- ☒ **US** United States of America.....
- ☒ **UZ** Uzbekistan .....
- ☒ **VN** Viet Nam .....
- ☒ **YU** Yugoslavia .....
- ☒ **ZA** South Africa .....
- ☒ **ZW** Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 22 April, 1998	PP3107	Australia		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

** Where the earlier application isan ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box:*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**

request	:	4
description (excluding sequence listing part	:	16
claims	:	4
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	25

This international application is **accompanied by** the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited micoorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ Other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the internationa application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

JONES, Paul for an on behalf of the applicants

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority specified by the applicant: ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

MEL G6\00110008.8

M·H

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

REC'D 16 FEB 2000
WIPO PCT

17

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PWJ:ag40126941	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. **PCT/AU 99/00294**	International filing date *(day/month/year)* 20 April 1999	Priority Date *(day/month/year)* 22 April 1998
International Patent Classification (IPC) or national classification and IPC **Int. Cl.**[7] A61K 031/545		
Applicant SOLTEC RESEARCH PTY LTD et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand 13 September 1999	Date of completion of the report 8 February 2000
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **G.R.PETERS** Telephone No. (02) 6283 2184

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU 99/00294

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , filed with the letter of .

[ ] the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , filed with the letter of .

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , filed with the letter of .

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , filed with the letter of .

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**YES**
	Claims **1-25**	**NO**
Inventive step (IS)	Claims	**YES**
	Claims **1-25**	**NO**
Industrial applicability (IA)	Claims **1-25**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

NOVELTY (N) and INVENTIVE STEP (IS) claims 1-25

- US 5 183 817 A
- US 4 866 067 A
- WO 8302555 A
- JP 07 048 230 A

Each of the citations disclose a composition for topical administration including at least 5% by weight piperidino pyrimidine, an acid, a solvent being either water or alcohol and also a co-solvent being either an aromatic or polyhydric alcohol, they also disclose a method of treating hair loss using the composition, consequently the claims are not novel and do not contain an inventive step.

The Industrial applicability of the claims is not in doubt

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: **40126941**

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/AU99/00294	**20 April 1999 20/04/99**	**22 April 1998 22/04/98**

Title of invention **Pharmaceutical composition**

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Soltec Research Pty Ltd
8 Marco Court
Rowville, Victoria 3178
AUSTRALIA

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Australia	**Australia**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WAI-CHIU SO, Tony
7 Marsden Crescent
Doncaster East, Victoria 3109
AUSTRALIA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Australia	**Australia**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DEO, Peter Paul
3/119 Atkinson Street
Oakleigh, Victoria 3166
AUSTRALIA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Australia	**Australia**

☐ Further applicants are indicated on a continuation sheet.

Sheet No. 2

International application No.
PCT/AU99/00294

Continuation of Box No. II **APPLICANT(S)**

If none of the following sub-boxes is used, this sheet should not to be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

TAIT, Russell John
33 Campbell Road
Deepdene, Victoria 3103
AUSTRALIA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Australia	**Australia**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/AU99/00294

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

NOONAN, Greg
CHERRY, James
DI GIANTOMASSO, Frank
CALLINAN, Keith
JONES, Paul
DAVY, John
TULLOCH, Debra

Freehills Patent Attorneys
Level 47
101 Collins Street
Melbourne, Victoria 3000
AUSTRALIA

Telephone No.:: **(613) 9288 1577**

Facsimile No.: **(613) 9288 1567**

Teleprinter No.:

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description
- ☐ as originally filed
- ☐ as amended under Article 34

the claims
- ☐ as originally filed
- ☐ as amended under Article 19 (together with any accompanying statement)
- ☐ as amended under Article 34

the drawings
- ☐ as originally filed
- ☐ as amended under Article 34

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Language for the purposes of international preliminary examination: English

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Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

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Sheet No. 4

International application No.
PCT/AU99/00294

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The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

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.....

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00294

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 031/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 031/505

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC AS ABOVE.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT: minoxidil, acid
CAPLUS: minoxidil, acid

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5183817A (BAZZANO) 2 February 1993 Column 24 lines 11-51.	1-25
X	US 4866067 (DI SCHIENA) 12 September 1989 Column 3.	1-25
X	WO 8302558A (BAZZANO) 4 August 1983 Page 8.	1-25

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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Date of the actual completion of the international search	Date of mailing of the international search report
13 May 1999	19 MAY 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer G.R.PETERS Telephone No.: (02) 6283 2184

INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 07048230A (JAPATIC ENGLISH LANGUAGE ABSTRACT) (HORIUCHI HIDEO et al) 21 February 1995.	1-25

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 99/00294

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
US 5183817	EP 71598, WO 8202833
US 4866067	None.
WO 8302558	US 5514672, US 5183817, EP 71598
JP 07048230	None

END OF ANNEX

PCT

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/505

A1

(11) International Publication Number: WO 99/53923

(43) International Publication Date: 28 October 1999 (28.10.99)

(21) International Application Number: PCT/AU99/00294

(22) International Filing Date: 20 April 1999 (20.04.99)

(30) Priority Data:
PP 3107 22 April 1998 (22.04.98) AU

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PHARMACEUTICAL COMPOSITION

(57) Abstract

A pharmaceutical composition for topical administration, including, as the pharmaceutically active component, at least 5 % by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof; an acid in an amount to completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof; a solvent composition including at least two of water, a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10 % by weight.

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PHARMACEUTICAL COMPOSITION

Background of the invention

The present invention relates to a vehicle system for a pharmaceutical composition comprising a piperidinopyrimidine derivative. More particularly minoxidil and to a pharmaceutical composition incorporating the vehicle system. Minoxidil is a pharmaceutically active ingredient having several indications including use as a hair growth stimulant.

Minoxidil has poor solubility in water and ethanol and pharmaceutical preparations currently marketed only contain a small percentage of minoxidil. That is, below 5%.

Numerous formulations comprising minoxidil have been published in the prior art including United States patents 4,139,619, 4,820,512, 5,104,646, 5,225,189, 4,938,953, 4,596,812, 5,006,332, 5,156,836 and 5,643,942. Many of the formulations require (or would require where the amount of minoxidil is greater than 5%) a very high percentage (often in the range of 30 to 50%) of propylene glycol or a similar glycol product in order to improve the solubility of minoxidil. Due to the viscosity and tack of propylene glycol, large amounts of propylene glycol or similar agents in a composition are not pharmaceutically or cosmetically elegant and may be unacceptable to the consumer. In addition, high concentrations of propylene glycol may cause local irritation and hypersensitivity upon application to the scalp.

It would accordingly be a significant advance in the art if a composition could be provided which would permit the inclusion of an increased percentage of the active ingredient, but without the disadvantages associated with a high propylene glycol concentration.

Accordingly, it is an object of the present invention to overcome, or at least alleviate, one or more of the difficulties and deficiencies related to the prior art. These and other objects and features of the present invention will be clear from

the following disclosure.

Summary of the invention

Accordingly, the present invention in a first aspect provides a pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight.

Applicants have surprisingly discovered that by adjusting the acid concentration of the composition the solubility of the piperidinopyrimidine derivatives may be significantly increased without the necessity of utilising large amounts of propylene glycol or optionally by excluding propylene glycol altogether. Accordingly the total amount of active in the composition may be significantly increased. In a preferred form, the pharmaceutically active component is present in amounts of approximately 5 to 25% by weight, preferably approximately 5 to 15% by weight, more preferably approximately 7.5 to 12% by weight.

Preferably the piperidinopyrimidine derivative is minoxidil. Preferably the minoxidil is present in the form of a salt. The salt may include acetate, citrate, succinate, benzoate, hydrochloride, sulphate, phosphate or lactate. Preferably an acetate or lactate salt of minoxidil is used. The acetate or lactate salts may exhibit enhanced solubility and improve the ability to incorporate increased amounts of the active component in the composition.

In a preferred form the acid is added in an amount sufficient to provide an

apparent pH to the composition of approximately 7.0 or less. The apparent pH of the composition is preferably between approximately 5.0 to 7.0, more preferably between 6.0 to 6.5. Any suitable acid may be used to adjust the pH, including mineral acids, such as hydrochloric acid, sulphuric acid, nitric acid and phosphoric acid, or organic acids such as citric acid, acetic acid, succinic acid, or maleic acid, or mixtures thereof. Acetic acid or lactic acid is preferred.

In a preferred form the acid is present at a level that provides at least 0.01 Normal acid. Alternatively, the acid is present in an amount equal to, or greater than, the amount of the piperidinopyrimidine derivative in Normal amounts.

Preferably the lower alcohol is ethanol. The ratio of water to ethanol is preferably from approximately 9:1 to 1;9, more preferably approximately 1:1 to 1:3, by volume.

Preferably, the co-solvent includes benzyl alcohol. The benzyl alcohol may be present in amounts of approximately 2.5 to 95% by weight, preferably approximately 5 to 40% by weight, based on the total weight of the pharmaceutical composition.

Alternatively, or in addition the co-solvent may include a polyhydric alcohol, for example a polyol selected from the group consisting of 1,3-butylene glycol, propylene glycol, preferably glycol 200 (PEG 200), polyethylene glycol 400 (PEG 400), hexylene glycol and dipropylene glycol, or glycerol. When propylene glycol is present, it may be present in amounts of approximately 10% by weight or less, preferably approximately 5% by weight, or less.

In compositions comprising 5% of minoxidil or greater, it is preferred to include benzyl alcohol in the composition. The benzyl alcohol may be present in amounts of up to 85% by weight, based on the total weight of the pharmaceutical composition.

In a preferred form the co-solvent system includes water and benzyl alcohol wherein the benzyl alcohol is in an amount of approximately 40 to 100% by

weight, based on the total weight of the co-solvent system.

In a preferred form the water is present in an amount no greater than 60% by weight.

In a preferred aspect, the pharmaceutical composition includes

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil acid salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

The final presentation of the composition may be any suitable topical pharmaceutical preparation and may include solutions, lotions, ointments, mousses, foams, sprays, aerosols, shampoos and/or conditioners, gels, creams, pastes, and other preparations known in the art. The composition may also include other ingredients such as preservatives, buffers, stabilisers, propellants and the like.

Preferably the pharmaceutical composition is a mousse composition. The mousse composition may include a suitable propellant, for example hydrocarbons or chlorofluorocarbons. Alternatively the pharmaceutical composition may be a gel composition. The gel composition may include a suitable gelling agent, e.g. a cellulose derivative. A hydroxy propyl cellulose, for example that sold under the trade designation Klucel M, has been found to be suitable.

Where an aerosol formulation is used, the aerosol formulation may be a homogeneous, aqueous-alcoholic emulsion system. The aerosol formulation upon actuation produces a stabilized, homogeneous, expandable foam which breaks easily with shear. A composition of this type is sometimes referred to as a "mousse".

In a further preferred aspect, the pharmaceutical composition according to

the present invention may further include an effective amount of a skin penetrating agent.

Suitable skin penetrating agents include alcohols such as dodecanol and oleyl alcohol; amines, such as isopropyl amine, diisopropyl amine, triethyl amine, triethanol amine, diisopropanolamine and ethylene diamine; carboxylic acids, such as oleic acid, linoleic acid and linolenic acid; esters, such as dibutyl sebacate, dibutyl phthalate, butyl benzoate and ethyl caprate; and others, such as Azone, N methyl pyrollidone, bile salts and urea.

All of the compositions herein may be actuated using propellants known per se in the pharmaceutical or cosmetic fields. Such propellants include hydrocarbons such as propane, isobutane or dimethyl ether and chlorofluorocarbons such as P-12, P114, and a 40:60 mixture thereof.

In the pharmaceutical composition according to the present invention, in addition to the above essential components, general purpose components ordinarily used in hair treatment compositions can be formulated, within a range which does not impair the effect of the present invention, including vitamins such as vitamin B.sub.6, vitamin E and derivatives thereof, and biotin; hair generating agents or hair generating aids such as panthothenic acid and derivatives thereof, glycylrrhetic acid and derivatives thereof, nicotinic acid esters such as benzyl nicotinate, cyclosporins, carpronium chloride, cepharanthine, oxendolone, diazoxide, minoxidil, and ethynylesteradiol; antibacterial agents such as hinokitiol, hexachlorophen, phenol, benzalkonium chloride, cetylpyridinium chloride, undecylenic acid, trichlorocarbanilide, and bithionol; refrigerants such as menthol; drugs such as salicylic acid, zinc and derivatives, thereof, and lactic acid and alkyl esters thereof; amino acids such as arginine; oil components such as olive oil, squalane, fluid paraffin, isopropyl myristate, higher fatty acids, and higher alcohols; perfumes; antioxidants; UV-ray absorbers; dyes; humectants; thickeners; perfumes; colour additives and the like.

In a still further aspect of the present invention, there is provided a method for the treatment of hair loss and related indications in humans, which method

includes

providing

a pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight; and

applying topically to the human scalp a therapeutically or prophylactically effective amount of the pharmaceutical composition.

The hair loss may be related to any of the forms of alopecia including male pattern alopecia. Related indications may include weakening of hair strength, loss of hair colour and the like.

Preferably the pharmaceutically active component includes a minoxidil or a minoxidil salt, more preferably a minoxidil acetate, succinate or citrate salt.

More preferably the pharmaceutical composition includes

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil acid salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

The present invention will now be more fully described with reference to the accompanying figures and examples. It should be understood, however, that the

description following is illustrative only and should not be taken in any way as a restriction on the generality of the invention described above.

In each of the following examples it was necessary to add an appropriate amount of acid to ensure equivalent acid normality. The standard technique for such an adjustment is to measure the apparent pH of the solution.

In the examples, the apparent pH of each formulation was measured once prepared. The measured taken as the apparent pH due to the high proportion of organic modifiers in the formulations. Typically, 0.5% (w/w) glacial acetic acid (0.1M) would be used in the formulation, which would equate to a pH of 1.0 in an aqueous system when no other components are contributing to the pH of the solution.

EXAMPLE 1

Topical Minoxidil lotion 5% with no propylene glycol

Minoxidil	5.00%
Ethanol	60.3%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	0.6
Purified Water	to total 100%

The apparent pH of the final formulated solution was measured at 6.24.

EXAMPLE 2

Topical Minoxidil mousse 5% for hair treatment

Minoxidil	5.00%
Cetyl Alcohol	2.20%
Stearyl Alcohol	1.00%
Ethanol	51.8
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Propylene Glycol	5.00%
Propellant P75	4.30%
Acetic Acid	qs. pH 6.0
Purified water	to total 100%

EXAMPLE 3

Topical Minoxidil lotion 8% for hair treatment

Minoxidil	8.00%
Ethanol	50.50%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Nitric Acid	qs. pH 6.0
Propylene Glycol	7.30%
Benzyl Alcohol	5.00%
Purified Water	to total 100%

EXAMPLE 4

Topical 8% (w/w) Minoxidil solution

Minoxidil	8.0%
Ethanol	50.5%
Crilet 3	0.4%
Teric 12A4	1.0%
Glacial Acetic Acid	0.3%
Propylene Glycol	7.5%
Benzyl Alcohol	5.0%
Purified Water	to total 100%

The apparent pH of the final formulated solution was measured at 6.24.

EXAMPLE 5

Topical Minoxidil lotion 10% for hair treatment

Minoxidil	10.00%
Ethanol	48.0%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Propylene Glycol	10.0%
Benzyl Alcohol	5.00%
Purified Water	to total 100%

EXAMPLE 6

Topical Minoxidil lotion 10% for hair treatment

Minoxidil	10.00%
Ethanol	47.50%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	15.00%
Purified Water	to total 100%

EXAMPLE 7

Topical 10% (w/w) Minoxidil solution

	Formulation 3a	Formulation 3b
Minoxidil	10.00%	10.00%
Ethanol	46.80%	44.20%
Crillet 3	0.4%	0.4%
Teric 12A4	1.0%	1.0%
Glacial Acetic Acid	1.0%	0.3%
Propylene Glycol	10.0%	nil
Benzyl Alcohol	5.00%	2.00%
Purified Water	to total 100%	to total 100%

The apparent pH of the final formulated solutions was measured at 6.0 and 6.5 for formulations 3a and 3b, respectively.

EXAMPLE 8

Topical Minoxidil lotion 11% for hair treatment

Minoxidil	11.00%
Ethanol	44.20%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	20.00%
Purified Water	to total 100%

EXAMPLE 9

Topical Minoxidil lotion 12% for hair treatment

Minoxidil	12.00%
Ethanol	42.7%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	20.00%
Purified Water	to total 100%

EXAMPLE 10

Topical Minoxidil lotion 12% for hair tr atment

Minoxidil	12.00%
Ethanol	42.7%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	10.00%
Propylene Glycol	10.00%
Purified Water	to total 100%

EXAMPLE 11

Topical Minoxidil lotion 12% for hair treatment

Minoxidil	12.00%
Ethanol	42.7%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	15.00%
Propylene Glycol	5.00%
Purified Water	to total 100%

There appear to be no obvious gross stability issues associated with any of the formulations. The levels of minoxidil were assayed in formulations 1 and 3a after they had been stored for one and three months at 4°C and 50°C. No measurable loss in potency was observed.

An aqueous gel was prepared by adding 0.75% (w/w) Klucel M (hydroxypropyl cellulose) to Example 4. The viscosity of the gel was measured at

2400 cPoise at 20°C.

EXAMPLE 12

Investigations were carried out to determine which of the components present in Example 7 (10% (w/w) minoxidil solution) were contributing to the solubilisation of minoxidil. The investigation was split into three sections:

- Effect of Co-solvent
- Effect of pH
- Effect of Salt

The solubility determination involved preparation of saturated solutions of minoxidil in the media of interest. These solutions were then filtered (0.45 µm) and analysed against a standard curve by means of direct UV spectroscopy.

Aqueous unbuffered solubility of Minoxidil

The aqueous solubility of minoxidil was found to be 2.2 mg/mL.

Effect of Co-solvent

The solubility of minoxidil was determined in each of the co-solvents, benzyl alcohol, glycerol, propylene glycol and ethanol. Additionally, the solubility of minoxidil was determined in 10% (w/w) solutions of each of the co-solvents, ethanol, propylene glycol and glycerol in water. A 4% (w/w) solution of benzyl alcohol was used since this was found to be the limit of the solubility of benzyl alcohol in water. The following table summarises the results of these studies.

Sample	Minoxidil S lubility (mg/mL)
Benzyl alcohol	125.1
Glycerol	47.3
Propylene Glycol	86.9
Ethanol	18.8
10% (w/w) Ethanol/Water	3.4
10% (w/w) Propylene Glycol/Water	3.0
4% (w/w) Benzyl Alcohol/Water	4.5
10% (w/w) Glycerol/Water	2.7

Analysis indicated that of the systems studied only the use of pure benzyl alcohol would result in the desired 10% (w/w) minoxidil solution.

Effect of apparent pH

Attempts were made to prepare saturated solutions of minoxidil in acetate buffers at apparent pH's 2.5, 3.5, 4.6, 5.0 and 6.0. Saturated solutions were achieved with those pHs above the pKa of minoxidil (4.61), the results of which are summarised in the following table.

pH	Minoxidil Solubility (mg/mL)
6.0	2.5
5.0	4.1
4.6	11.3

It was not possible to determine the solubility limits of minoxidil at pH's below it's pKa, as minoxidil was found to be extremely soluble in acidic media and the buffer used had insufficient capacity to avoid the drift in pH observed with additions of minoxidil to the solution. The maximum minoxidil concentration studied was 22 mg/mL and was found to be completely soluble in pH 2.5 and 3.5 solutions at this concentration. The following table outlines the maximum solubility that would be expected in an acidic aqueous media knowing the solubility of the

base form of minoxidil is 2.2 mg/mL and assuming infinite solubility of the acid form of minoxidil.

pH	Minoxidil Solubility (mg/mL)
3.6	22.0
3.0	87.6
2.6	220.0
2.0	876.0

Effect of Salt

Minoxidil base was used for these studies with the appropriate salt (acetate or HCl) formed *in situ*. As discussed above the use of low pH acetate buffers significantly increased the solubility of minoxidil.

The major factors affecting the solubilisation of minoxidil in an aqueous environment were found to be:

The type and proportion of co-solvents present in the formulation

The pH of the final formulated solution

The amount of minoxidil used

The acid form of minoxidil has been shown to be much more soluble in an aqueous environment. The use of co-solvents has been shown to enhance the solubility of the minoxidil free base. The co-solvents may also enhance the solubility of the acid form. The use of an appropriate salt enhances the solubility of the acid form of minoxidil. Therefore, a combination of these three factors may be used to optimise the solubility of minoxidil in a topical solution based formulation.

All the above examples were stored at room temperature and no crystallisation or precipitation was observed for at least 10 days.

Please note all percentages are based upon the total weight of the

composition unless otherwise specified.

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

It will also be understood that the term "comprises" (or its grammatical variants) as used in this specification is equivalent to the term "includes" and should not be taken as excluding the presence of other elements or features.

CLAIMS

1. A pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight.

2. A pharmaceutical composition according to Claim 1, wherein the acid is added in an amount sufficient to provide an apparent pH to the composition of approximately 7.0 or less.

3. A pharmaceutical composition according to Claim 1, wherein the pharmaceutically active component is present in an amount of from approximately 5 to 25% by weight, based on the total weight of the pharmaceutical composition.

4. A pharmaceutical composition according to Claim 3, wherein the pharmaceutically active component is present in an amount of approximately 7.5 to 12% by weight, based on the total weight of the pharmaceutical composition.

5. A pharmaceutical composition according to Claim 1, wherein the pharmaceutically active component is minoxidil or a salt thereof.

6. A pharmaceutical composition according to Claim 2, wherein the acid provides to the composition an apparent pH in the range of approximately 5.0 to 7.0.

7. A pharmaceutical composition according to Claim 2, wherein the acid is a

mineral or organic acid.

8. A pharmaceutical composition according to Claim 7, wherein the acid includes acetic or lactic acid.

9. A pharmaceutical composition according to Claim 1, wherein the solvent composition includes water and ethanol in a range of approximately 1:1 to 1:3 by volume.

10. A pharmaceutical composition according to Claim 1, wherein the co-solvent includes benzyl alcohol.

11. A pharmaceutical composition according to Claim 1, wherein the solvent composition system includes water and benzyl alcohol wherein the benzyl alcohol is in an amount of approximately 40 to 100% by weight based on the total weight of the co-solvent system.

12. A pharmaceutical composition according to Claim 1, wherein the water is present in an amount no greater than approximately 60% by weight based on the total weight of the co-solvent system.

13. A pharmaceutical composition according to Claim 1, wherein the co-solvent includes an alkylene glycol.

14. A pharmaceutical composition according to Claim 13, wherein the alkylene glycol is selected from one or more of the group consisting of glycerol, 1,3-butylene or propylene glycol.

15. A pharmaceutical composition according to Claim 1, wherein the acid is present at a level that provides at least 0.01 Normal acid.

16. A pharmaceutical composition according to Claim 1, wherein the acid is present in an amount equal to or greater than the amount of the piperidinopyrimidine derivative in Normal amounts.

17. A pharmaceutical composition according to Claim 1, wherein the solvent system includes water and ethanol in a range of approximately 9:1 to 1:9 by volume.

18. A pharmaceutical composition according to Claim 5, wherein the pharmaceutically active component is a minoxidil salt.

19. A pharmaceutical composition according to Claim 18, wherein the minoxidil salt is a minoxidil acetate or lactate salt.

20. A pharmaceutical composition according to Claim 1, including

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil acid salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

21. A method for the treatment of hair loss and related indications in humans, which method includes

providing

a pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight; and

applying topically to the human scalp a therapeutically or prophylactically

effective amount of the pharmaceutical composition.

22. A method according to Claim 21, wherein the pharmaceutically active component includes minoxidil or a minoxidil salt.

23. A method according to Claim 22, wherein the minoxidil salt is a minoxidil acetate or lactate salt.

24. A method according to Claim 21, wherein the pharmaceutical composition includes

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

25. A pharmaceutical composition according to Claim 1, substantially as herein before described with reference to any one of the examples.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00294

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 031/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 031/505

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC AS ABOVE.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT: minoxidil, acid
CAPLUS: minoxidil, acid

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5183817A (BAZZANO) 2 February 1993 Column 24 lines 11-51.	1-25
X	US 4866067 (DI SCHIENA) 12 September 1989 Column 3.	1-25
X	WO 8302558A (BAZZANO) 4 August 1983 Page 8.	1-25

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 1999	19 MAY 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer G.R.PETERS Telephone No.: (02) 6283 2184

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00294

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 07048230A (JAPATIC ENGLISH LANGUAGE ABSTRACT) (HORIUCHI HIDEO et al) 21 February 1995.	1-25

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 99/00294

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
US 5183817	EP 71598, WO 8202833
US 4866067	None.
WO 8302558	US 5514672, US 5183817, EP 71598
JP 07048230	None

END OF ANNEX

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rul s 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
P.Q. 12,774		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/01281	26/04/1999	25/04/1998
Applicant		
CENTRAL RESEARCH LABORATORIES LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01281

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see annexed sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8

   Method of split-and-pool synthesis of a plurality of products wherein at least some of the synthesis articles are labelled with an identifying code indicating the synthesis history after the penultimate synthesis step.

2. Claims: 9,10

   Apparatus for labelling an article comprising means for isolating an individual article, a laser beam, and means for directing the laser beam with respect to the surface of the article so as to form a label thereon.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01281

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01J19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 24061 A (ONTOGEN CORPORATION) 8 August 1996 (1996-08-08) abstract page 15, line 32 - page 16, line 12 page 18, line 5 - line 27 page 20, line 16 - page 21, line 14 page 29, line 18 - line 31 page 30, line 6 - line 17 page 39, line 12 - line 20 page 40, line 1 - line 30 claim 49; figures	1,2,5,6, 11
A	---	3,4,7,8
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 1999	16. 08. 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stevnsborg, N

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01281

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 36436 A (IRORI) 21 November 1996 (1996-11-21) abstract page 60, line 25 - line 28 page 77, line 13 - line 15 page 82, line 15 - page 84, line 28 figures 1,8	9,10
A	---	1-8,11
P,X	WO 98 53093 A (BIOARAY SOLUTIONS LLC & RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY) 26 November 1998 (1998-11-26) abstract claims 1,8; figure 1	1,2,5,6, 11

A	WO 97 19958 A (WLODEK MANDECKI) 5 June 1997 (1997-06-05) abstract page 2, line 26 - line 36 page 4, line 23 - page 5, line 14	1-8,11

A	WO 92 09300 A (ITEREX PHARMACEUTICALS LTD. PARTNERSHIP) 11 June 1992 (1992-06-11) page 51, line 8 - page 52, line 23 claim 35; figures 1A,1B	1,2,4-6, 11

A	US 4 631 211 A (RICHARD A. HOUGHTEN) 23 December 1986 (1986-12-23) abstract column 7, line 31 - column 8, line 39 claims 1,20; figures 1-4	1,2,4-6, 11

A	GB 2 306 484 A (UNIVERSITY OF HERTFORDSHIRE) 7 May 1997 (1997-05-07) cited in the application abstract	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/01281

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 9715390 A	01-05-1997